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OFFICE OF
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MEMORANDUM

SUBJECT: **Lindane**; P.C. Code 009001. The HED Toxicology Chapter for the Risk Assessment for the Reregistration Eligibility Decision Document (RED), Case # 818566. DP Barcode: D269338

From: Suhair Shallal, Toxicologist
Reregistration Branch 4
Health Effects Division (7509C)

Thru: Sanjivani Diwan, Senior Toxicologist
Reregistration Branch 4
Health Effects Division (7509C)
and
Susan V. Hummel, Branch Senior Scientist
Reregistration Branch 4
Health Effects Division (7509C)

To: Suhair Shallal, Risk Assessor
Reregistration Branch 4
Health Effects Division (7509C)

Attached is the Toxicology Chapter for lindane, for purposes of issuing a Reregistration Eligibility Decision (RED) Document.

LINDANE

PC Code: 009001

Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision Document

Date: September 28, 2000

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1.0 HAZARD CHARACTERIZATION

Lindane is a moderately toxic compound in EPA toxicity class II. Labels for products containing it must bear the Signal Word WARNING. It is neither an eye nor dermal sensitizer. Some formulations of lindane are classified as Restricted Use Pesticides (RUP), and as such may only be purchased and used by certified pesticide applicators. Lindane is no longer manufactured in the U.S., and most agricultural and dairy uses have been canceled by the EPA because of concerns about the compound's potential to cause cancer.

The primary effect of lindane is on the nervous system; as seen in both acute, subchronic, and developmental neurotoxicity studies, as well as, combined chronic and carcinogenicity study, lindane appears to cause neurotoxic effects including tremors, convulsions and hypersensitivity to touch. This is further corroborated by the published literature in which human exposure has been seen to produce neurologic effects. Lindane also causes renal and hepatic toxicity via the oral, dermal and inhalation routes of exposure as seen in subchronic, reproduction and chronic toxicity studies in the rat.

In developmental toxicity studies, no developmental effects were seen at levels where maternal toxicity was evident. In the rat developmental study, the developmental effects (extra rib and total skeletal variations) were seen at dose levels (20 mg/kg/day) greater than those that elicit maternal toxicity (10 mg/kg/day). In the reproduction study, both systemic and developmental LOAELs are 13 mg/kg; however a qualitative difference in maternal and offspring effects (reduced body weight of maternal animals and reduced viability and delayed maturation in pups) indicates an increased pup susceptibility to exposure to lindane. This is further corroborated by a developmental neurotoxicity study in which a qualitative and quantitative increase in susceptibility is seen. At the high dose (13.7 mg/kg/day) , parental animals have a reduced body weight and body weight gain while at the mid-dose (5.6 mg/kg/day) offspring have a reduced survival rate, decreased body weights and body weight gains during lactation, increased motor activity, and decreased motor activity habituation as compared to controls. The FQPA factor was therefore reduced to 3X.

The toxicity endpoints have been selected by the Hazard Identification Assessment Review Committee (HIARC, 7/00) and can be found in Section 8- Appendices. They include acute and chronic reference doses (RfDs), and short-, intermediate- and long-term dermal and inhalation no observable adverse effect levels (NOAELs). A reassessment of the cancer classification will occur after a review of the new mouse carcinogenicity report due in December 2000. Currently, according to the TES committee report (1994), lindane has not been classified by the HED Cancer Peer Review Committee. The RfD/Peer Review Committee (1993) concluded that: "The mouse carcinogenicity data were considered insufficient because of major deficiencies associated with all studies available." Lindane however had been previously (1985) classified by the Cancer Assessment Group of the Office of Research and Development as a group B2/C carcinogen based on increased incidence of mouse liver tumors. The upper-bound slope of the dose-response as reported in the memorandum is $Q1^* = 1.1\ (mg/kg/day)^{-1}$.

Lindane does not appear to be mutagenic. The available mutagenicity studies are negative; they include a dominant lethal mutation assay, sister chromatid exchange assay and mammalian cell culture gene mutation in V79 cells. IPCS (1991) reported that lindane does not appear to have mutagenic potential.

There is some evidence that lindane may act as an endocrine disruptor; further investigation is necessary to ascertain the relevance and impact of such findings on public health.

2.0 REQUIREMENTS

The requirements (CFR 158.340) for food-use for LINDANE are in Table 1.

Table 1.[A]

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	-
870.3150	Oral Subchronic (nonrodent)	yes	-
870.3200	21-Day Dermal	-	-
870.3250	90-Day Dermal	yes	yes
870.3465	90-Day Inhalation	yes	yes
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	-
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	no
870.4300	Chronic/Oncogenicity		
870.5100	Mutagenicity—Gene Mutation - bacterial		
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5915	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	-
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b	90 Day Neuro. Screening Battery (rat)	yes	yes
870.6300	Develop. Neuro	yes	yes
870.7485	General Metabolism		
870.7600	Dermal Penetration	yes	yes
Special Studies for Ocular Effects			
	Acute Oral (rat)	no	-
	Subchronic Oral (rat)	no	-
	Six-month Oral (dog)	no	-

[A] Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

3.0 DATA GAP(S)

A Mouse Carcinogenicity Study is expected in December 2000.

4.0 HAZARD ASSESSMENT

4.1 Acute Toxicity

Adequacy of data base for acute toxicity: The data base for acute toxicity is considered complete. No additional studies are required at this time. Lindane is a moderately toxic compound in EPA toxicity class II. It is neither an eye nor dermal sensitizer. The vehicle used when administering lindane can determine its toxicity. It appears that oily solutions of lindane are more toxic than ones suspended in water. Clinical signs including convulsions, spasms as well as death have been found to occur after administration of lindane. The acute toxicity data on LINDANE is summarized below in Table 2.

Table 2. Acute Toxicity Data on LINDANE

Guideline No./ Study Type	MRID No.	**Results**	**Toxicity Category**
870.1100 Acute oral toxicity	00049330	LD_{50} 88 mg/kg - males 91 mg/kg - females	II
870.1200 Acute dermal toxicity	00109141	LD_{50} 1000 mg/kg - males 900 mg/kg - females	II
870.1300 Acute inhalation toxicity	Acc. 263946	LC_{50} 1.56 mg/L both sexes	III
870.2400 Acute eye irritation	Acc. 263946	PIS = 0.6 no corneal involvement irritation cleared after 24 hours	III
870.2500 Acute dermal irritation	Acc. 263946	PIS = 0 not an irritant	IV
870.2600 Skin sensitization	Acc. 263946	not a sensitizer	NA

4.2 Subchronic Toxicity

Adequacy of data base for subchronic toxicity: The data base for subchronic toxicity is considered complete due to the availability of chronic studies and subchronic neurotoxicity study. No additional studies are required at this time.

Lindane appears to affect the liver and kidney in male rats when administered through the oral, dermal or inhalation routes of exposure. In addition, in an oral neurotoxicity study, hypersensitivity to touch and hunched posture were the basis for a neurotoxicity LOAEL of 28.1 mg/kg.

870.3100 90-Day Oral Toxicity - Rat

The requirements for subchronic oral studies are satisfied by chronic oral studies. See chronic oral section for executive summaries.

870.3100 90-Day Oral Toxicity - Mouse

The requirements for subchronic oral studies are satisfied by chronic oral studies. See chronic oral section for executive summaries.

870.3150 Oral Toxicity - Dog

Chronic studies in two species, rat and rabbit, are available. See chronic oral section for executive summaries.

870.3200 90-Day Dermal Toxicity – Rat

EXECUTIVE SUMMARY: In a subchronic dermal toxicity study (MRID 41427601), groups of 40 male and 40 female New Zealand white rabbits were treated with lindane (99.5% a.i.) in 5% aqueous carboxymethyl cellulose at doses of 0, 10, 60, or 400 mg/kg/day. Due to excessive toxicity the high dose was reduced to 350 mg/kg/day from week nine and to 320 mg/kg/day from week eleven. Animals were treated by dermal occlusion for 6 hours/day, 5 days/week. Within each dose group, 10 animals/sex were used for interim sacrifice at week 6, 20 animals/sex were used for the main study and dosed for 13 weeks, and 10 animals/sex were dosed for 13 weeks and allowed a 6 week recovery period.

Tremors and convulsions were observed in high-dose animals beginning after day 16 in males and after day 19 in females. One mid-dose female displayed these clinical signs on day 50 only. Clinical signs of toxicity were not observed in low-dose animals. Reactions at the site of application were not reported. In the high-dose group, 17 males and 8 females died prior to scheduled sacrifice. Deaths were first observed after week 5. All animals in the control, low-, and mid-dose groups survived to scheduled sacrifice.

Body weights and body weight gains by the low- and mid-dose males and females were similar to the controls throughout the study. High-dose males and females began to lose weight after the first week of the study resulting in absolute body weights 3-7% and 3-10%, respectively, lower than the controls during the 13 weeks of treatment. During recovery, body weights of the males remained 3-8% below the controls while females recovered to 1-3% lower than the controls. Body weight data were not analyzed statistically. Body weight loss by the high-dose groups correlated with generally reduced food consumption during treatment.

No treatment-related effects were observed on ophthalmology, urinalysis, or white blood cell parameters. Alkaline phosphatase activity was significantly increased in high-dose animals at interim sacrifice for females (+34%; p # 0.05), and at main study sacrifice for males (+44%; p # 0.01) and females (+53%; p # 0.01). High-dose females also had significantly increased (-glutamyl transferase activity (+38%; p # 0.01) at main study sacrifice. For high-dose males, significant (p # 0.05 or 0.01) reductions in hemoglobin (-7%), RBC (-8.6%), and PCV (-5.7%) were observed at main study sacrifice. These red cell parameters were comparable to the controls after recovery. Red cell parameters in females were not affected.

At main study sacrifice, high-dose males and females had slightly increased absolute kidney weights and significantly (p # 0.01) increased relative kidney weights as compared with the controls. Absolute and relative kidney (left and right) weights were 104-106% and 112-114%, respectively, for males and 105-106% and 115-116%, respectively, for females. High-dose females also had significantly (p # 0.01) increased absolute (+27.01 to 27.24%) and relative (+30.53 to 44.985) liver weights at both interim and main study sacrifice which remained slightly (+13 to 17.31%; n.s.) elevated after recovery. Relative liver weights were significantly (+36.77%; p # 0.01) increased for high-dose males at main study sacrifice. Absolute adrenal weights (left and right) were significantly (p # 0.05 or 0.01) increased at main study sacrifice for mid-dose males (+19.5 to 23.4%), high-dose males (+40.5 to 46.3%), and high-dose females (+33 to 34%). Relative adrenal weights were increased (p # 0.05 or 0.01) +19 to 21.6% for mid-dose males and +46 to 56.9% for high-dose males and females. Following the recovery period, organ weights of the treated groups were similar to the control group.

No treatment-related gross or histopathological lesions were observed in the kidneys, adrenals, or skin. The incidence and severity of centrilobular hypertrophy of the liver was increased in mid- and high-dose males and females at the interim, main, and recovery sacrifice times. At both the interim and main sacrifices, centrilobular hypertrophy was observed in 20% of mid-dose males, 25-30% of mid-dose females, 80-100% of high-dose males and 73-90% of high-dose females. Following recovery this lesion was seen in 30% and 40% of mid-dose males and females, respectively, and in 50% and 29% of high-dose males and females, respectively.

Therefore, the dermal toxicity LOAEL is >400 mg/kg/day and the dermal toxicity NOAEL is not identified. The systemic toxicity LOAEL is 60 mg/kg/day based on histopathological lesions of the liver in males and females and increased adrenal weights of males. The systemic toxicity NOAEL is 10 mg/kg/day.

This study is classified as **Acceptable/guideline** and does satisfy the guideline requirements for a repeated-dose dermal study (82-2) in rabbits.

870.3465 90-Day Inhalation – Rat

<u>EXECUTIVE SUMMARY:</u> In a subchronic inhalation toxicity study (Accession No. 255003), lindane (99.9% a.i., Batch no. 79044/174) was administered by inhalation to groups of 12 male and 12 female Wistar rats at nominal concentrations of 0, 0.02, 0.10, 0.50, or 5.0 mg/m^3, 6 h/day for 90 days. Additional control and high concentration groups, 12 rats/sex, were treated for 90 days and allowed to

recover for 6 weeks before sacrifice. Analytically measured atmospheric concentrations were 0, 0.02, 0.12, 0.60, and 4.54 mg/m^3, respectively. The arithmetic mean particle size of the aerosol was 1.11±0.39 : m and the geometric mean was 1.03±1.45 : m.

Lindane was detected in the brain, liver, fat, and serum of all exposed rats. The chemical accumulated in fat with levels reaching 127,120 : g/g and 58,260 : g/g in high-dose females and males, respectively. After the recovery period, traces of lindane were still detectable in the tissues.

All rats survived to scheduled sacrifice. "Slight" diarrhea and piloerection were observed in all males and females exposed to the highest concentration, but the time to onset and duration were not included. No exposure-related effects were noted for body weight gain, food consumption, water consumption, or urinalysis parameters. Although hematology parameters did not appear to be affected by treatment, no individual animal data were included and the statistics could not be verified. Clinical chemistry results, especially for Na^+, K^+, and Ca^{++}, were highly variable. Cytochrome p-450 in males and females exposed to 5 mg/m^3 was 338% and 174%, respectively, of the control values after 90 days, but similar to the control levels after the recovery period.

Bone marrow myelograms from animals exposed to 5 mg/m^3 showed significantly (p # 0.05) increased reticulocytes (+108%), stem cells (+31%), and myeloblasts (+33%) in males,and increased reticulocytes (+55) in females, and decreased (-45%) lymphocytes in females. However, these changes in bone marrow cannot be definitively attributed to treatment since bone marrow from the other exposed groups was not assayed.

Males exposed to 5 mg/m^3 had significantly (p # 0.05 or 0.01) increased absolute (+7.8% to +11.7%) and relative (+19.1% to 19.2%) kidney weights as compared with the controls. Absolute and relative kidney weights in the males exposed to 0.5 mg/m^3 were increased by 8-9.8% and 6.9-8.2%, respectively. Although not statistically significant, the increases in kidney weights for these groups were considered biologically significant. After the recovery phase, kidney weights from the exposed males were similar to the controls. In females exposed to 5 mg/m^3 absolute and relative kidney weights were increased (p # 0.05) by 9.2-9.9% and 7.9-8.2%, respectively, as compared with the controls.

In high-dose males, absolute liver weights were not affected, but relative liver weights were slightly (6.9%) higher than the controls. For females exposed to the highest dose, absolute and relative liver weights were 12.2% and 11.0% higher, respectively, than the controls. No differences in absolute and relative liver weights were noted between the exposed and control groups after the recovery period.

Kidney lesions in males exposed to 0, 0.02, 0.10, 0.50, or 5.0 mg/m^3, were observed in 17%, 0, 25%, 83% and 82%, respectively, of the animals. These lesions included cloudy swelling of the tubule epithelia, dilated renal tubules with protein containing contents, and proliferated tubules. After the recovery phase, only cloudy swelling of the tubule epithelia was observed in two control animals and one high-concentration animal.

Therefore, the systemic toxicity LOAEL is 0.50 mg/m^3 (0.13 mg/kg) based on transient microscopic lesions in the kidney and increased kidney weights of male rats. The systemic toxicity NOAEL is 0.1 mg/m^3 (0.025 mg/kg).
This study is considered **Acceptable/guideline** and satisfies the requirement for a subchronic inhalation toxicity study in rats [82-4].

870.6200 Subchronic oral neurotoxicity– Rat
See Section 4.8 Neurotoxicity for Executive Summary

4.3 Prenatal Developmental Toxicity

Adequacy of data base for Prenatal Developmental Toxicity: The data base for prenatal developmental toxicity is considered complete. No additional studies are required at this time.
Lindane is not considered teratogenic when administered orally or subcutaneously. Developmental NOAELs were found to be at levels equal to or greater than maternal NOAELs, except in the Developmental Neurotoxicity Study. The neurotoxicity LOAEL was 5.6 mg/kg/day (NOAEL is 1.2 mg/kg/day) based on reduced pup survival, decreased body weights and body weight gains during lactation, increased motor activity, and decreased motor activity habituation compared to a maternal toxicity LOAEL of 13.7 mg/kg/day (NOAEL is 5.6 mg/kg/day) based on decreased body weight gains, decreased food consumption, and increased reactivity to handling.

870.3700a Prenatal Developmental Toxicity Study - Rat
EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 42808001), 20 presumed pregnant CFY (derived from Charles River CD) rats per group were administered technical lindane (purity not given; Batch No. 6801/403) by gavage in 0.5% carboxymethyl-cellulose at doses of 0, 5, 10, and 20 mg/kg/day on gestation days (GD) 6-15, inclusive. On GD 20, dams were sacrificed by CO_2, subjected to gross necropsy, and all fetuses examined externally. Approximately one-third of each litter was processed for visceral examination and the remaining two-thirds was processed for skeletal examination.

Deaths of two high-dose dams were attributed by the authors to treatment although the cause of death was not reported. No treatment-related clinical signs of toxicity were observed in any animal. Body weight gains and food consumption by the mid- and high-dose groups were decreased during the treatment interval as compared with the controls. Body weight gains by the mid- and high-dose dams were 70% and 46%, respectively, of the control values during GD 6-14. Food consumption by the mid- and high-dose groups was 72% of the control level during GD 7-10 and 92% and 65%, respectively, during GD 11-14. It should be noted that data were not available for the entire dosing interval and that statistical analyses were not provided for these data.

Maternal necropsy was unremarkable. Organ weights were similar between the treated and control groups.

Therefore, the maternal toxicity LOAEL is 10 mg/kg/day based on reduced body weight gain and food consumption. The maternal toxicity NOAEL is 5 mg/kg/day.

No significant differences were observed between the control group and the treated groups for number of corpora lutea, number of implantation sites, live fetuses/dam, pre- and post-implantation losses, fetal body weights, or fetal sex ratios. No treatment-related effects were found at external or visceral examination of the fetuses.

The percentage of litters in the control, low-, mid-, and high-dose groups containing fetuses with extra (14th) ribs was 12.7, 21.0, 31.7, and 40.6% (p # 0.05), respectively. The total incidences of litters containing fetuses with skeletal variants were 43.4, 52.7, 59.5, and 68.0% (p # 0.01), respectively. Although the response rates in the high-dose group for extra ribs and total variants are within the upper limit of historical control data, they were considered treatment-related due to the dose-related manner of increase.

Therefore, the developmental toxicity LOAEL is 20 mg/kg/day based on increases in extra ribs and total skeletal variants; a trend for increases in these endpoints at the lower doses is recognized. The developmental toxicity NOAEL is 10 mg/kg/day.

Although, this study was conducted prior to implementation of current guidelines but is considered sufficient for the purpose for which it was intended. This study is classified as **Acceptable/nonguideline** and satisfies the requirements for a developmental toxicity study (83-3a) in rats. Several deficiencies were noted in the conduct of this study: percent purity of the test article wast not given, less than 20 litters/group were available, dosing solutions were not analyzed for concentration, stability, or homogeneity, and much of the individual animal data were not included.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 00062656), groups of presumed pregnant Sprague-Dawley rats were administered lindane (purity not given; Lot No. 36346) by subcutaneous injection in corn oil (1 ml/kg) at doses of 0, 5, 15, or 30 mg/kg/day on gestation days (GD) 6-15, inclusive. On GD 19, dams were sacrificed and the fetuses removed. Approximately one-third of the fetuses from each litter were sectioned and examined for visceral malformations/variations. The remaining two-thirds of each litter were "examined externally" and processed and examined for skeletal malformations/variations.

Two high-dose animals died prematurely. Clinical signs of toxicity, including tremors, convulsions, urine stains, excitability, and anorexia, were reported for one high-dose animal. However, it was not possible to correlate clinical signs with death since individual animal data were not included. No other clinical signs of toxicity were reported. Body weight gains by the mid- and high-dose dams were 76% and 23%, respectively, of the control levels during the treatment interval with both groups attaining statistical significance (p # 0.05). Overall body weight gain by the high-dose group was 69% (p # 0.05) of the controls. Food consumption by the high-dose group was 47% of the control level during GD 6-11. Body weight gains by the low-dose group and food consumption for the low- and mid-dose groups were similar to the controls throughout the study. Gross necropsy data, other than uterine data, for the dams were not provided.

Therefore, the maternal toxicity LOAEL is 15 mg/kg/day based on decreased body weight gain. The maternal toxicity NOAEL is 5 mg/kg/day.

No treatment-related effects were observed between the control group and the treated groups for number of corpora lutea, number of implantation sites, live fetuses/dam, pre- and post-implantation losses, fetal body weights, or fetal crown-rump lengths. No treatment-related visceral or skeletal malformations/variations were observed in any of the fetuses. Results of external examination were not reported.

Therefore, the developmental toxicity NOAEL is >30 mg/kg/day and the developmental toxicity LOAEL was not identified.

This study is classified as **Unacceptable/nonguideline** and does not satisfy the requirements for a developmental toxicity study (83-3a) in rats. Several deficiencies were noted in the conduct of this study: the subcutaneous route is not the preferred method of administration, percent purity of the test article was not given, dosing solutions were not analyzed for concentration, stability, or homogeneity, less than 20 litters/group were available for evaluation, and much of the individual maternal and fetal data were not included. However, this data may be used as supplemental information.

870.3700b Prenatal Developmental Toxicity Study - Rabbit

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 42808002), 13 presumed pregnant New Zealand white rabbits per group were administered lindane (purity not given; Batch No. 6801/403) by gavage in 0.5% carboxymethyl-cellulose at doses of 0, 5, 10, or 20 mg/kg/day on gestation days (GD) 6-18, inclusive. On GD 29, dams were sacrificed, subjected to gross necropsy, and all fetuses examined for visceral and skeletal malformations/variations. Data from external examination of the fetuses was not included.

All does survived to scheduled sacrifice. No treatment-related clinical signs of toxicity were observed. Maternal body weight and food consumption were similar between the treated and control groups. Gross necropsy was unremarkable. Organ weights were similar between the treated and control groups.

Therefore, the maternal toxicity NOAEL is >20 mg/kg/day and the maternal toxicity LOAEL was not identified.

No treatment-related effects were observed in any dose group for number of corpora lutea, number of implantation sites, live fetuses/dam, pre- and post-implantation losses, fetal body weights, or fetal sex ratios. No treatment-related visceral or skeletal malformations/variations were observed in any of the fetuses.

Therefore, the developmental toxicity NOAEL is >20 mg/kg/day and the developmental toxicity LOAEL was not identified.

This study is classified as **Unacceptable/not upgradable** and does not satisfy the requirements for a developmental toxicity study (83-3b) in rabbits. Maternal and developmental toxicity LOAELs were not identified and the highest dose did not approach the limit dose. Therefore, dose selection was considered inadequate. Doses were based on the results of a subcutaneous study in the rabbit (MRID 00062658) which is not a valid method for selecting doses for an oral study. Several other deficiencies were noted in the conduct of this study: percent purity of the test article was not given, dosing solutions were not analyzed for concentration, stability, or homogeneity, and much of the individual animal data were not included.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 00062658), 15 presumed pregnant New Zealand white rabbits per group following artificial insemination were administered lindane (purity and Batch No. not given) by subcutaneous injection in corn oil (0.5 ml/kg) at doses of 0, 5, 15, or 45 mg/kg/day on gestation days (GD) 6-18, inclusive. Due to excessive toxicity, the high dose was reduced to 30 mg/kg/day after GD 9. On GD 29, dams were sacrificed, subjected to gross necropsy, and all fetuses examined for visceral and skeletal malformations/variations. Data from external examination of the fetuses was not included.

One mid-dose dam aborted and died on GD 21 and 14/15 high-dose animals died between GD 10 and 26. The high-dose group was then discontinued due to excessive mortality. Decreased activity and immobilized rear quarters were observed in the mid-dose group (frequency and number affected not reported). No clinical signs of toxicity were observed in the low-dose group. During GD 6-20, does in the mid-dose group had a body weight loss of 126.7 g as compared with a body weight gain of 218.0 g by the controls. Body weight loss was accompanied by “markedly lower” food consumption by the mid-dose animals. Body weight changes and food consumption for the low-dose group were similar to the controls throughout the study.

It appeared that does in the mid- and high-dose group had differences in the texture of the liver, however, data from gross necropsy were difficult to interpret due to poor copy quality of the original report.

Therefore, the maternal toxicity LOAEL is 15 mg/kg/day based on clinical signs of toxicity, death, and reduction in body weight. The maternal toxicity NOAEL is 5 mg/kg/day.

No treatment-related effects were observed between the control group and the treated groups for number of corpora lutea, number of implantation sites, live fetuses/dam, pre- and post-implantation losses, fetal body weights, or fetal crown-rump distances. No treatment-related visceral or skeletal malformations/variations were observed in any of the fetuses. Abortion by one mid-dose doe was assumed to be due to excessive maternal toxicity and not to a direct effect on the embryos or fetuses.

Therefore, the developmental toxicity NOAEL is >15 mg/kg/day and the developmental

toxicity LOAEL was not identified.

This study is classified as **Unacceptable/not upgradable** and does not satisfy the requirements for a developmental toxicity study (83-3b) in rabbits. Several deficiencies were noted in the conduct of this study: the subcutaneous route is not the preferred method of administration, excessive toxicity occurred at the high-dose, percent purity of the test article wast not given, dosing solutions were not analyzed for concentration, stability, or homogeneity, and much of the individual maternal and fetal data were not included. However, these study results may be used in conjunction with the oral developmental toxicity study in rabbits (MRID 42808002) as supplemental information.

870.6300 Developmental Neurotoxicity Study - Rat
See Section 4.8 Neurotoxicity for Executive Summary

4.4 Reproductive Toxicity

Adequacy of data base for Reproductive Toxicity: The data base for reproductive toxicity is considered complete. No additional studies are required at this time. Both parental and offspring LOAELs are 13 mg/kg; however there is a qualitative difference in the severity of effects. In the parental animals, toxicity was seen in the form of reduction in body weight gain during gestation while offspring toxicity was correlated with decreases in pup viability and pup body weight in the F_1 and F_2 generations as well as delayed maturation in the F_2 generation. Evidence for quantitative increase in susceptibility could not be ascertained due to the wide spread in the doses tested.

870.3800 Reproduction and Fertility Effects - Rat
EXECUTIVE SUMMARY: In a multigeneration reproductive toxicity study (MRID 42246101), lindane (99.5% a.i.; Batch No. DA433) was administered to groups of 30 male and 30 female Charles River CD rats at dietary concentrations of 0, 1, 20, or 150 ppm (0.087, 1.71, and 13.05 mg/kg/day, respectively) during the per mating period for two generations. One litter was produced in each generation. F_1 pups chosen as parental animals were weaned onto the same diet as their parents. Test or control diets were administered to the F_0 and F_1 parental animals for 71 and 70 days, respectively, before the animals were mated within the same dose group. All animals were continuously exposed to test material either in the diet or during lactation until sacrifice.

Premature sacrifices or intercurrent deaths of two F_0 animals and five F_1 animals were considered incidental to treatment; all other F_0 and F_1 males and females survived to terminal sacrifice. No treatment-related clinical signs of toxicity were observed in males or females of either generation at any time during the study. No treatment-related effects on body weights, body weight gains, food consumption, or food efficiency were observed for the F_0 and F_1 males and females during premating. Gross necropsy and histopathology of females was unremarkable.

During gestation days 10-13, mean body weight gain by the high-dose F_0 females was significantly reduced (11%). Mean body weight gains by the high-dose F_0 females were also significantly lower on lactation day 1 (interval not specified) as compared to the controls, but recovery was apparent by weaning. No treatment-related changes in body weights or body weight gains were observed in the F_1 females during gestation or lactation.

High-dose male rats of both generations had a significantly (p # 0.01) increased incidence of pale kidneys (10/29 F_0 males and 10/30 F_1 males) as compared with the controls (0/30 and 0/28, respectively). Areas of change on the kidneys (not defined) were observed in 7/29 high-dose F_0 males compared with 2/30 controls and in 4/30 mid-dose F_1 males and 5/30 high-dose F_1 males compared with 1/28 controls. Significantly ($p \leq 0.01$) increased incidence of hydronephrosis was observed in high dose F_1 males (7/30) as compared to controls (0/28). Absolute and relative kidney weights of the mid- and high-dose F_0 males and the high-dose F_1 males were significantly (p # 0.01) increased as compared with the controls.

F_0 and F_1 males in the mid- and high-dose groups had significantly (p # 0.01) increased incidences of chronic interstitial nephritis, cortical tubular cell regeneration, hyaline droplets in proximal tubules, tubular necrosis with exfoliation and cellular casts, and cortical tubular casts (n.s.). These changes are characteristic of alpha 2μ globulin accumulation, which is specific to male rats.

Increased absolute and relative liver weights, accompanied by hepatocellular hypertrophy, in the mid- and high-dose males and females of both generations were considered adaptive and of no biological significance.

Therefore, the LOAEL for systemic toxicity is 150 ppm (13.05 mg/kg/day) based on decreased body weight gains by the F_0 females during gestation. The systemic toxicity NOAEL is 20 ppm. In addition, the LOAEL for male rats is 20 ppm (1.71 mg/kg/day) based on increased kidney weights and histopathological lesions in the kidney characteristic of alpha 2: globulin accumulation; the NOAEL for males is 1 ppm (0.087 mg/kg/day).

Mating, fertility, gestation survival (postimplantation index), and liveborn indices, mean precoital interval, and mean gestation length were similar between the treated and control groups of both generations. The sex distribution was not affected by the test material. Mean litter sizes of the treated groups were not different from the controls throughout lactation for both generations. Viability indices for the high-dose F_1 and F_2 pups were 81% and 85%, respectively, compared with $96% for the controls. This reduction in survival on lactation day 4 was due to the death or sacrifice (for humane reasons) of three F_1 litters and two F_2 litters. No treatment-related clinical signs of toxicity were observed in the pups of either generation during lactation. Pup necropsy was unremarkable.

Body weights of the low- and mid-dose F_1 and F_2 pups were similar to the controls throughout lactation. Body weights of the high-dose pups of both generations were significantly (p # 0.01) less than the controls on lactation days 1 and 25. In high-dose F_2 pups, the onset and completion of tooth eruption and completion of hair growth were significantly (p # 0.01) delayed 10.5%, 11.6%, and 24%, respectively, as compared with the controls.

Therefore, the LOAEL for reproductive toxicity is 150 ppm (13.05 mg/kg/day) based on reduced pup body weights and decreased viability in both generations and delayed maturation of the F_2 pups. The reproductive toxicity NOAEL is 20 ppm (1.71 mg/kg/day).

This study is classified as **Acceptable/guideline** and satisfies the guideline requirements for a reproduction study (83-4) in rats. No major deficiencies were identified in the conduct of this study.

4.5 Chronic/ Carcinogenicity Toxicity

Adequacy of data base for chronic toxicity: The data base for chronic toxicity is considered complete. No additional studies are required at this time. The liver appears to be the major target organ. The incidence of periacinar hepatocytic hypertrophy was significantly (p # 0.01) increased in the 100- and 400-ppm (4.81 and 6.00 mg/kg/day, respectively) males and the 400-ppm females at 30 days and 26 weeks. In addition, increased liver and spleen weights, and decreased platelets were also noted.

Kidney lesions in males indicative of alpha 2: globulin accumulation were observed in animals treated with $10 ppm, but are not considered relevant to human health risk assessment.

870.4100a (870.4300) Chronic Toxicity – Rat

EXECUTIVE SUMMARY: Results from interim sacrifice of 15 rats/sex/group, at 30 days and 26 weeks, of an ongoing chronic/oncogenicity study are presented in this report (MRID 41094101). In the chronic toxicity/oncogenicity study (MRID 41853701), lindane (99.75% a.i., Lot no. DA433) was administered in the diet to groups of 115 male and 115 female Wistar rats at concentrations of 0, 1, 10, 100, or 400 ppm for 2 years. Corresponding delivered doses were 0, 0.05, 0.47, 4.81, and 19.66 mg/kg/day, respectively, for males and 0, 0.06, 0.59, 6.00, and 24.34 mg/kg/day, respectively, for females.

No clinical signs of toxicity were observed. Mortalities in the 0, 1, 10, 100, and 400 ppm groups included 1, 2, 2, 2, and 0 males, respectively, and 2, 0, 1, 1, and 8 females, respectively. Deaths in high-dose females occurred during weeks 2-4 and the cause of death was not determined. Body weights were slightly less than the controls for the high-dose males (-6%) and females (-8%) during weeks 1-5 of the study, but gradually increased to within 2% of the control level by week 26 for males and week 9-10 for females. Food consumption was “marginally lower” in high-dose males and females and water consumption was “marginally higher” in high-dose males (63 ml/kg/day versus 50 ml/kg/day for controls).

High-dose females had significantly (p # 0.01) decreased hemoglobin (-4 to -7%) at weeks 3, 12, and 24, decreased RBC counts (-6 to -6.3%) at weeks 3 and 24, and decreased PCV (-4.2 to -9.1%) at weeks 3 and 24. These red cell parameters were “marginally lower” for high-dose males, but statistical significance was not reached. Platelet counts were increased by up to 13-14% in mid- (not defined) and high-dose males (week 12) and females (week 24). White cell counts were significantly (p # 0.05) increased 27.5% in mid-dose (not defined) and 23.5% in high-dose females due to increases in neutrophils.

Statistically significant (p # 0.05 or 0.01) changes in clinical chemistry parameters were observed in high-dose males and females during the first 24 weeks. Inorganic phosphorous was increased by 7.3-29% and calcium was increased by 3.5-10%. Females in the 1, 10, and 100 ppm groups also had significantly (+6 to +8%; p # 0.01) increased calcium levels at week 3 as compared with the controls. Differences in urea and total cholesterol by the high-dose males and females were not consistent over time and did not appear to be dose-related.

Urinalyses were conducted by routine analysis, after water deprivation, and after water loading. Differences in urinalysis parameters between treated and control females were considered random and not treatment-related. No clear evidence of an effect on kidney function was observed in males.

Absolute kidney weights were significantly (p # 0.05 or 0.01) increased in high-dose males by 12.9% and 39.3%, and relative kidney weights were increased by 27.3% and 43.0% at 30 days and 26 weeks, respectively. Absolute and relative kidney weights from the 100-ppm males were increased by 16.9% and 23.6%, respectively, at 30 days, but were similar to the controls at 26 weeks.

Absolute liver weights were significantly (p # 0.01) increased by 40.8% in high-dose males at 26 weeks and by 29.3% and 32.3% in high-dose females at 30 days and 26 weeks, respectively. Relative liver weights of the high-dose males and females were significantly (p # 0.05 or 0.01) were greater (14.0-37.2%) than the controls at both sacrifice times.

Increases in the incidence of pale kidneys in 100- and 400-ppm males were noted at necropsy. At both 30 days and 26 weeks hyaline droplets in the proximal tubules were observed in the kidneys of all males (10/10; p# 0.01) receiving 10, 100, and 400 ppm compared with none of the controls. Tubular regeneration (p # 0.01) was observed after 30 days in 9-10/10 males treated with $10 ppm, but at 26 weeks was seen in only 8/10 males given 100 ppm and 7/10 given 400 ppm. In the 100 and 400 ppm groups, interstitial chronic nephritis occurred in 5-6 males at 30 days and 26 weeks and cortical tubular necrosis was observed in 9-10 males at 30 days. At 26 weeks cortical tubular necrosis was seen in only 2 100-ppm males and 5 (p # 0.05) 400-ppm males. These treatment-related kidney lesions were not observed in control males or in females at any dose level.

The incidence of periacinar hepatocytic hypertrophy was significantly (p # 0.01) increased in the 100- and 400-ppm males and the 400-ppm females at 30 days and 26 weeks. At 30 days the incidences were 7/10 and 10/10 for males, respectively, and 9/9 for females. After 26 weeks of treatment, the incidences were 8/10 and 10/10 for males, respectively, and 9/9 for females. This lesion was not seen in control animals of either sex. No treatment-related histopathological lesions were observed in the spleen, adrenals, brain, or thymus. Bone marrow data presentation was inadequate for assessment.

Therefore, the systemic toxicity LOAEL is 10 ppm (0.59 mg/kg/day) based on microscopic lesions in the kidney of male rats. The systemic toxicity NOAEL is 1 ppm (0.06 mg/kg/day).

This study is considered **Acceptable/nonguideline** as an interim report for a combined chronic toxicity/oncogenicity study in rats [83-5]. It is sufficient for the purpose for which it was intended as an interim report.

EXECUTIVE SUMMARY: In a chronic toxicity/oncogenicity study (MRID 41853701), lindane (99.75% a.i., Lot no. DA433) was administered in the diet to groups of 50 male and 50 female Wistar rats at concentrations of 0, 1, 10, 100, or 400 ppm for 2 years. Corresponding delivered doses were 0, 0.05, 0.47, 4.81, and 19.66 mg/kg/day, respectively, for males and 0, 0.06, 0.59, 6.00, and 24.34 mg/kg/day, respectively, for females. An additional 15 rats/sex/group were designated for interim sacrifices at 30 days and 26 weeks (the results from these interim sacrifices are presented separately (MRID 41094101); more sacrifices were performed at 52 and 78 weeks.

Clinical signs of toxicity consisted of convulsions in 11 high-dose females. No other clinical signs were observed. Survival at the end of the study was 36, 36, 31, 20, and 16% for males and 49, 38, 44, 35, and 18% for females in the 0, 1, 10, 100, and 400 ppm groups, respectively. Survival of high-dose males was similar to the controls through week 93. For females, however, survival was significantly decreased in the high-dose group with 50% survival reached at week 89 compared to week 104 for the control group.

Body weight gains were significantly (p # 0.01) decreased for the 100- and 400-ppm males during the first few weeks of the study as compared to the controls. Because final body weights of the 100 ppm males were similar to the controls, the initial reduction in weight gain was not considered biologically significant. Final body weights of the high-dose males were significantly (-14%; p # 0.05) less than the controls. Body weights and body weight gains for the treated females were similar to the controls throughout the study. Food consumption by the high-dose groups was decreased 15% in males and 19% in females during the first week of the study, however, total food consumption for the entire study was similar to the control levels.

Platelet counts were significantly (p # 0.05 or 0.01) increased (20% or less) in the 100- and 400-ppm males at week 12 and in 100- and 400-ppm males and females at week 24, but not at later time points. High-dose males and females had significant (p # 0.05 or 0.01) decreases in red blood cell parameters at week 104 as compared with the controls: hemoglobin was -15.6% and -17.6%, respectively, erythrocyte counts were -14.1% and -21%, respectively, and PCV was -15.9% and -18.2%, respectively.

Significant (p # 0.05 or 0.01) changes in clinical chemistry parameters were observed in high-dose males and females during the first year of the study. Inorganic phosphorous was increased by 7.3-38.5% and calcium was increased by 3.4-10% in males and females; cholesterol was increased by 45-110% and urea was increased by 20-54% in females; and the albumin/globulin ratio was decreased by 8.3-18.2% in females. All parameters were similar to the control levels by week 104.

High-dose males and females had increased absolute and relative liver weights at all interim sacrifices, although statistical significance was not always reached. At study termination, absolute and relative liver weights were significantly (p # 0.01) increased by 21.2% and 38.5%, respectively, in high-dose males and by 31.6% and 33.5%, respectively, in high-dose females. At 100 ppm, absolute liver weights were increased by 8.6-11.2% (n.s.) and relative liver weights were increased by 14.4-17.6% (p # 0.05 or 0.01) for both sexes at week 104. Significant (p # 0.05 or 0.01) increases in absolute and relative spleen weights at week 52 and in relative spleen weights at week 104 were also noted, but the sex was not identified. The incidence rate of periacinar hepatocytic hypertrophy was significantly increased in the 100- and 400-ppm groups with 25/50 males and 19/50 females affected at 100 ppm and 40/50 males and 43/50 females affected at 400 ppm. No treatment-related histopathological lesions were observed in the spleen or bone marrow.

Kidney lesions in males indicative of alpha 2: globulin accumulation were observed in animals treated with $10 ppm, but are not considered relevant to human health risk assessment.

Therefore, the systemic toxicity LOAEL for male and female rats is 100 ppm (4.81 and 6.00 mg/kg/day, respectively) based on periacinar hepatocyte hypertrophy, increased liver and spleen weights, and decreased platelets. The systemic toxicity NOAEL is 10 ppm.

Among high-dose males, there was an apparent increase in adrenal pheochromocytomas. The percentage of animals with tumors (benign and malignant) was 14, 12, 19, 14, and 26% in the 0, 1, 10, 100, and 400 ppm groups, respectively. Statistical significance can be shown depending on the test used. Based on the data presented in this study, an assessment of the carcinogenic potential of lindane cannot be made. Additional histopathological examination of the adrenals from animals in the 1, 10, and 100 ppm groups, as well as historical control data for this tumor type, are required. These data were submitted as a separate study (MRID 42891401).

This chronic toxicity/oncogenicity study in the rat is **Unacceptable/upgradable** and does not satisfy the guideline requirement for a combined chronic toxicity/oncogenicity study in rats [83-5]. Additional data on adrenal pheochromocytomas is necessary to complete the assessment.

<u>EXECUTIVE SUMMARY:</u> The current study (MRID 42891201) was submitted as supplemental information to the combined chronic toxicity/oncogenicity study. Data from additional microscopic examination of the adrenal gland from males in the low- and two mid-dose groups and historical control data are included. In a chronic toxicity/oncogenicity study (MRID 41853701), lindane (99.75% a.i., Lot no. DA433) was administered in the diet to groups of 50 male and 50 female Wistar rats at concentrations of 0, 1, 10, 100, or 400 ppm for 2 years. Corresponding delivered doses were 0, 0.05, 0.47, 4.81, and 19.66 mg/kg/day, respectively, for males and 0, 0.06, 0.59, 6.00, and 24.34 mg/kg/day, respectively, for females. An additional 15 rats/sex/group were designated for interim sacrifices at 30 days and 26 weeks; the results from these interim sacrifices are presented separately (MRID 41094101).

Clinical signs of toxicity consisted of convulsions in 11 high-dose females. No other clinical signs were observed. Survival at the end of the study was 36, 36, 31, 20, and 16% for males and 49, 38, 44, 35, and 18% for females in the 0, 1, 10, 100, and 400 ppm groups, respectively. Survival of high-dose males was similar to the controls through week 93. For females, however, survival was significantly decreased in the high-dose group with 50% survival reached at week 89 compared to week 104 for the control group.

Body weight gains were significantly (p # 0.01) decreased for the 100- and 400-ppm males during the first few weeks of the study as compared to the controls. Because final body weights of the 100 ppm males were similar to the controls, the initial reduction in weight gain was not considered biologically significant. Final body weights of the high-dose males were significantly (-14%; p # 0.05) less than the controls. Body weights and body weight gains for the treated females were similar to the controls throughout the study. Food consumption by the high-dose groups was decreased 15% in males and 19% in females during the first week of the study, however, total food consumption for the entire study was similar to the control levels.

Platelet counts were significantly (p # 0.05 or 0.01) increased (20% or less) in the 100- and 400-ppm males at week 12 and in 100- and 400-ppm males and females at week 24, but not at later time points. High-dose males and females had significant (p # 0.05 or 0.01) decreases in red blood cell parameters at week 104 as compared with the controls: hemoglobin was -15.6% and -17.6%, respectively, erythrocyte counts were -14.1% and -21%, respectively, and PCV was -15.9% and -18.2%, respectively.

Significant (p # 0.05 or 0.01) changes in clinical chemistry parameters were observed in high-dose males and females during the first year of the study. Inorganic phosphorous was increased by 7.3-38.5% and calcium was increased by 3.4-10% in males and females; cholesterol was increased by 45-110% and urea was increased by 20-54% in females; and the albumin/globulin ratio was decreased by 8.3-18.2% in females. All parameters were similar to the control levels by week 104.

High-dose males and females had increased absolute and relative liver weights at all interim sacrifices, although statistical significance was not always reached. At study termination, absolute and relative liver weights were significantly (p # 0.01) increased by 21.2% and 38.5%, respectively, in high-dose males and by 31.6% and 33.5%, respectively, in high-dose females. At 100 ppm, absolute liver weights were increased by 8.6-11.2% (n.s.) and relative liver weights were increased by 14.4-17.6% (p # 0.05 or 0.01) for both sexes at week 104. Significant (p # 0.05 or 0.01) increases in absolute and relative spleen weights at week 52 and in relative spleen weights at week 104 were also noted, but the sex was not identified.

The incidence rate of periacinar hepatocytic hypertrophy was significantly increased in the 100- and 400-ppm groups with 25/50 males and 19/50 females affected at 100 ppm and 40/50 males and 43/50 females affected at 400 ppm. No treatment-related histopathological lesions were observed in the spleen or bone marrow.

Kidney lesions in males indicative of alpha 2: globulin accumulation were observed in animals treated with $10 ppm, but are not considered relevant to human health risk assessment.

Therefore, the systemic toxicity LOAEL for male and female rats is 100 ppm (4.81 and 6.00 mg/kg/day, respectively) based on periacinar hepatocyte hypertrophy, increased liver and spleen weights, and decreased platelets. The systemic toxicity NOAEL is 10 ppm (0.47 and 0.59 mg/kg/day, males and females, respectively).

Eight additional males were identified as having adrenal pheochromocytomas. The revised percentages of animals with adrenal tumors in the 0, 1, 10, 100, and 400 ppm groups are 14, 16, 16, 6, and 24% for benign tumors, respectively, and 0, 0, 6, 8, and 2% for malignant tumors, respectively. Statistical significance was not reached by relevant tests. For comparison, historical control data from Charles River and publications in the open literature were submitted. The 10 and 100 ppm groups had malignant tumor incidence rates greater than the historical control rate (0-2%). The high-dose group also had a slight excess of benign and combined tumor rates as compared with the historical control rates (8-22% benign, combined could not be calculated), but this same net tumor incidence was the same as the control group of a published study. In the current study, pheochromocytomas were not considered the cause of death for any animal with the exception of a single animal in the 100 ppm group.

Therefore, no evidence dose-related and statistically significant increase in adrenal tumors was observed in this study. The study was conducted at adequate dose levels.

This chronic toxicity/oncogenicity study in the rat is **Acceptable/guideline (revised)** and satisfies the guideline requirement for a combined chronic toxicity/oncogenicity study in rats [83-5].

870.4100b Chronic Toxicity - Dog

Chronic studies in two species, rat and rabbit, are available. See chronic oral section for executive summaries.

4.6 Carcinogenicity

Adequacy of data base for Carcinogenicity: The data base for carcinogenicity is considered incomplete. According to the TES committee report (1994), lindane has not been classified by the HED Cancer Peer Review Committee. It was determined by the RfD/Peer Review Committee (1993) that: "The mouse carcinogenicity data were considered insufficient because of major deficiencies associated with all studies available." Lindane however had been previously (1985) classified by the Cancer Assessment Group of the Office of Research and Development as a group B2/C carcinogen based on increased incidence of mouse liver tumors. The upper-bound slope of the dose-response was given in that memorandum as $Q1^* = 1.1$ (mg/kg/day)$^{-1}$. A mouse carcinogenicity study is expected to be submitted in December 2000.

870.4200a Carcinogenicity Study - rat

See the chronic toxicity section for executive summaries

870.4200b Carcinogenicity (feeding) - Mouse
A new study is expected in December 2000.

EXECUTIVE SUMMARY: In a special study, (MRID none) three strains of female mice, agouti, pseudoagouti, and black, were administered lindane at dietary concentrations of 0 or 160 ppm. The doses were selected based on a preliminary study where no deaths occurred after one month. Groups of 36-96 animals per strain were continuously fed treated or control diets for up to 24 months. Additional groups of 48-96 agouti and black mice were fed treated or control diets for 6 months then fed control diet for 6 or 18 months (recovery).

No clinical signs of toxicity and no survival information were reported. No apparent effects on body weights or food consumption were observed, but only limited data were presented. When compared with untreated controls at 6 and 12 months, benzo(a)pyrene monooxygenase activity in the liver was increased 1.61-1.84x in the agouti, 2.71-2.78x in the pseudoagouti, and 2.07-2.09x in the black strains.

Liver weights were increased 14.7-31.2% in the agouti, 13.5-22.0% in the pseudoagouti, and 12.2-16.4% in the black strains at interval sacrifices up to 24 months. Following the recovery period, liver weights of the treated mice were similar to the controls.

No evidence for increased incidence or decreased latency of liver tumors was observed for the black strain at any time during the study (24 months) or for the pseudoagouti strain through the 18 month sacrifice. At 18 months, 0/34 control and 12/36 (33%) of the treated agouti mice developed hepatocellular adenomas; one carcinoma each in the treated and control groups was noted. Both the treated agouti and pseudoagouti strains had clear increases in adenomas and slight increases in carcinomas at 24 months. The incidence rates for the control and treated agouti groups were 9% and 35%, respectively, for adenomas and 13% and 17%, respectively, for carcinomas. The incidence rates for the control and treated pseudoagouti groups were 5% and 12%, respectively, for adenomas and 2% and 5%, respectively, for carcinomas.

Increases in Clara cell hyperplasia were noted in the lung at all sacrifice intervals for each strain and the incidence of lung tumors was increased in later months for the agouti and pseudoagouti strains. The percentage of mice with Clara cell hyperplasia in the control and treated groups was 6-31% and 72-92%, respectively, for the agouti; 6-17% and 50-79%, respectively, for the pseudoagouti; and 0-14% and 56-90%, respectively, for the black. Lung tumors for the agouti strain occurred in 0% of the control and 17% of the treated animals at 18 months and 4% of the control and 19% of the treated animals at 24 months. Lung tumors in the pseudoagouti strain occurred in 6% of the controls and 14% of the treated animals at 24 months. After recovery, the incidences of Clara cell hyperplasia (agouti and black) and lung tumors (agouti) remained slightly elevated as compared with the controls.

In conclusion, dietary administration of lindane resulted in the induction of liver and lung tumors in the agouti and pseudoagouti mouse strains and caused increased liver weights, increased enzyme activity, and irreversible Clara cell hyperplasia in the lung of all three mouse strains tested.

This study is considered **Acceptable/nonguideline** as a special study in mice. The study deficiencies include: only females tested, only one dose level tested, histopathology data provided for lung and liver only, lack of analytical chemistry data, and no individual animal data. These study results can be used as supplementary information to the chronic/oncogenicity study in rats.

4.7 Mutagenicity

Adequacy of data base for Mutagenicity: The data base for Mutagenicity is considered adequate based on submitted studies and reports in the open literature. Lindane does not appear to be mutagenic. In a mammalian cell gene mutation assay and an in vivo sister chromatid exchange assay, no mutagenic response was detected. The open literature suggests, however, that technical grade HCH (hexachlorohexane; 6.5% (-HCH) may induce some mutagenic activity as evidenced in a dominant lethal mutation assay and sister chromatid exchanges. Overall, based on the results of acceptable studies on lindane, it does not appear to have mutagenic potential.

Gene Mutation

Guideline #, cell gene mutation assay MRID 00144500 **Unacceptable/Guideline**	In a mammalian cell gene mutation assay conducted in Chinese hamster V79 cells, lindane was tested in the absence of metabolic activation at dose levels of 2.5, 5, 10, 25, 50, 70, 100, and 150 :g/ml and in the presence of metabolic activation at dose levels of 5, 10, 25, 50, 100 250 and 500 :g/ml. The S9 fraction used for metabolic activation was obtained from Aroclor 1254-induced mouse liver. Tests with and without activation were conducted under aerobic and anaerobic conditions. Under anaerobic conditions, lindane without S9 was cytotoxic to the V79 cells at dose levels above 10 :g/ml and with S9 at dose levels above 150 mg/ml. **No mutagenic activity of lindane was observed in V79 cells** under any combination of conditions up to cytotoxic doses.

Cytogenetics

Guideline #, sister chromatid exchange MRID 00024504 **Acceptable/Guideline**	In a mammalian *in vivo* sister chromatid exchange (SCE) assay, 50:g tablets of bromodeoxy-uridine were implanted into male and female CF-1 mice. Two hours after implantation, lindane was administered *ip* in arachis oil at dose levels of 1.3, 6.4 and 32.1 mg/kg. For each dose level and control group, 30 bone marrow cells from each of 5 animals of each sex were examined for SCEs. No toxicity was reported in any treatment group. When results for male and female animals were pooled, only the highest dose produced a significant increase in SCEs over the controls. Positive control values were appropriate.

Guideline #, dominant lethal assay MRID 00062657 **Unacceptable/Guideline**	In a mammalian dominant lethal assay, 10 male Sprague-Dawley rats of unspecified age per group were exposed to lindane administered by subcutaneous injection in corn oil at doses of 0, 1, 3, and 10 mg/kg five time per week for 10 weeks. Uteri were examined for live and dead implants and abnormalities. Males were also sacrificed and gross pathological analysis performed. The incidence of dead implants was significantly increased at the lowest dose but not at the two higher doses in the first week of mating but this increase was not observed during the second week. **The authors conclude that lindane did not cause an increase in the incidence of dominant lethals in this study.**

4.8 Neurotoxicity

Adequacy of data base for Neurotoxicity: Neurotoxicity studies (acute, subacute and developmental) have been submitted. Lindane is a neurotoxicant. In acute, subchronic and developmental neurotoxicity studies, it was found to cause neurotoxic effects including tremors, convulsions, decreased motor activity, increased forelimb grip strength, hypersensitivity to touch, hunched posture and decreased motor activity habituation. There also appears to be a greater susceptibility to exposure by offspring compared to parental animals. The LOAEL for offspring toxicity is 50 ppm (5.6 mg/kg/day) based on reduced pup survival, decreased body weights and body weight gains during lactation, increased motor activity, and decreased motor activity habituation compared to a LOAEL of 120 ppm (13.7 mg/kg/day) based on decreased body weight gains, decreased food consumption, and increased reactivity to handling for maternal toxicity.

870.6100 Delayed Neurotoxicity Study - Hen
Not required

870.6200 Acute Neurotoxicity Screening Battery
EXECUTIVE SUMMARY: In an acute oral neurotoxicity study (MRID 44769201), groups of 10 Crl:CD®BR rats/sex/dose were administered single dose of lindane (Batch No. HLS96/1, Purity 99.78%) by gavage at concentrations of 0 (control), 6, 20, or 60 mg/kg. Functional observational battery (FOB) and motor activity (MA) testing were performed prior to administration and within 3 hours (time of peak effect) of dosing (day 0), and on days 7 and 14 post-dose. Body weights were recorded pre-test, weekly during the study period and on FOB assessment days. Clinical signs were recorded at least once daily. At study termination all animals were sacrificed and fixed by whole body perfusion, designated tissues of the nervous system were processed for microscopic neuropathological evaluation.

All animals survived to scheduled termination. One male in the 60 mg/kg group was observed to convulse on the day of treatment within 2.75 hours after dosing. Clinical signs were also observed in females treated at 60 mg/kg within 24 hours of dosing and included: staining of the fur, stained urogenital region, hunched posture, and piloerection. These effects in females persisted for four days. Significant treatment-related decreases in body weight gains were observed for males in the 60 mg/kg group compared to the control group for the first week of the study. Females administered this concentration also had slightly lower body weight gains throughout the study. Food consumption for males and females administered 60 mg/kg was significantly decreased compared to controls for Week 1 of the study. Food conversion ratios in the treated groups were not changed compared to control groups.

At the first FOB assessment on Day 0 (3 hours after dosing) males and females in the 60 mg/kg group exhibited piloerection (1 %, 2 &), decreased rectal temperature (1 %, 1 &), increased hindlimb foot splay and hunched posture (4 %, 7 &). Among males dosed at 60 mg/kg, increased respiration (3 %, 1 &) and one observation of tremor/twitching were observed. Females administered 60 mg/kg were observed to have increased incidences of walking on tip toes (10), licking behavior (3), decreased foot splay (3) and an absence of grooming (8) behavior. Females in the 20 mg/kg also had decreased grooming (3) behavior and increased forelimb grip strength. Motor activity was significantly decreased for males and females treated with 60 mg/kg as well as among females treated with 20 mg/kg three hours post-treatment. The 6 mg/kg group remained comparable to controls in FOB assessment parameters and MA.

No neuropathological endpoints were observed during the histological examinations of the peripheral or central nervous systems of these animals at any exposure concentration.

The NOAEL for systemic toxicity is 20 mg/kg for males and 6 mg/kg for females. Based on the substance-related effects on body weight, body weight gain, food consumption, and clinical signs of toxicity the LOAEL for systemic toxicity in males is 60 mg/kg. The LOAEL for females is 20 mg/kg based on a lower incidence of grooming behavior and decreased locomotor activity immediately after dosing, in addition to the parameters mentioned above.

The NOAEL for neurotoxic effects is 6 mg/kg for females and the LOAEL is 20 mg/kg based on increased forelimb grip strength and decreased grooming behavior and motor activity (MA). The NOAEL for neurotoxicity in males is 20 mg/kg and the LOAEL for males is 60 mg/kg based on tremors, convulsions, decreased MA, and increased forelimb grip strength.

This study is classified **Acceptable/guideline** and satisfies the Subdivision F guideline requirement for an acute oral neurotoxicity study (§81-8) in rats.

870.6200 Subchronic Neurotoxicity Screening Battery

<u>EXECUTIVE SUMMARY</u>: In a subchronic oral neurotoxicity study (MRID 44781101), groups of 10 Crl:CD®BR rats/sex/group were administered lindane (Batch No. HLS96/1, Purity 99.78%) in the diet for 13 weeks at concentrations of 0 (control), 20, 100, or 500 ppm. Due to severe toxic reactions to treatment at 500 ppm, the dose was reduced to 400 ppm on day 11 of treatment thereafter. These doses resulted in average daily intake values of 0, 1.4, 7.1, and 28.1 mg/kg/day for males and 0, 1.6, 7.9, and 30.2 mg/kg/day in females for 0, 20, 100, and 500/400 ppm, respectively. Functional observational battery (FOB) and motor activity (MA) tests were performed prior to administration and after 4, 8, and 13 weeks of treatment. Body weights were recorded pre-test, weekly during the study period and on FOB assessment days. Clinical signs were recorded at least once daily. At study termination all animals were sacrificed and fixed by whole body perfusion and designated tissues of the nervous system were

processed for microscopic neuropathological evaluation.

Three females in the 500/400 group died prior to scheduled termination. These deaths were attributed to treatment with lindane. One death was recorded on Day 11 of the study, one during week 10 and one during week 13. Clinical signs prior to death included weight loss, swollen muzzle with scabbing, hunched posture, piloerection, and staining of the anogenital region. Observations in surviving females treated at 500/400 ppm were hypersensitivity to touch, staining of the urogenital region, and scabbing of the toes.

Significant treatment-related decreases (p<0.05 or p<0.01) in body weight were observed among males and females treated with 500/400 ppm of 14% and 23%, respectively. Decreases in body weight gains (70% **%** and 180% **&**, p<0.01), food consumption (35% **%** and 50% **&**, p<0.05 or p<0.01, respectively), and food conversion ratios were observed for males and females in the 500 ppm groups compared to the control group for the first week of the study. Male rats tended to recover from these effects after the dose was lowered. Females, however, did not exhibit this same level of recovery as their food consumption remained slightly depressed throughout the remainder of the study.

Females in the 100 ppm group had significantly decreased body weight gains (40%, p<0.05) compared to the control group during the first week of the study and this effect continued, although not at a level of significance throughout the remainder of the study. Females in the 100 ppm group had significantly decreased food consumption (16%, p<0.01) for the first week of the study and this trend continued throughout the study. Liver weights were also found to be increased at 500/400 ppm for both sexes; no additional information was given.

During the FOB assessment (table A is attached at the end of this document), males and females treated at the highest dose (500/400 ppm) were perceived as difficult to handle. They also were observed to have piloerection and hunched posture. Females in the highest dose group had missing claws (3), tended to urinate more often than controls, had a higher incidence of grooming behavior, rearing, motor activity, and one female was observed to convulse. Females across the dose groups were observed walking on tiptoes (5-7) and these incidences were significantly increased compared to the control (1) for the highest dose group. Females (5) in the 100 ppm group also had increased incidences of grooming behavior at the Week 4 evaluation and one animal in this group was extremely difficult to handle.

The assessments of forelimb and hindlimb grip strength as well as hindlimb splay revealed no differences for any of the treated groups compared to the control groups. Colburn motor activity was also similar among treated groups compared to the control groups.

No neuropathological endpoints attributable to lindane administration were observed during the histological examinations of the peripheral or central nervous systems of these animals at any exposure concentration.

The NOAEL for systemic toxicity is 100 ppm for males (7.1 mg/kg) and 20 ppm for females (1.6 mg/kg). Based on the substance-related effects on body weight, body weight gain, food consumption, and clinical signs of toxicity the LOAEL levels for systemic toxicity in males is 500/400 ppm (28.1 mg/kg)and 100 ppm for females (7.9 mg/kg).

The NOAEL for neurotoxic effects is 100 ppm for males (7.1 mg/kg) and females (7.9 mg/kg). The neurotoxicity LOAEL is 500/400 ppm based on hypersensitivity to touch and hunched posture.

This study is classified **Acceptable/guideline** and satisfies the Subdivision F guideline requirement for an acute oral neurotoxicity study (§81-8) in rats.

870.6300 Developmental Neurotoxicity Study

EXECUTIVE SUMMARY: In a developmental neurotoxicity study (MRID 45073501), lindane (Batch No. HLS 96/1; 99.78% a.i.) was administered to presumed pregnant Hsd Brl Han:Wist (Han Wistar) rats in the diet at concentrations of 0, 10, 50, or 120 ppm from gestation day (GD) 6 through lactation day 10. These concentrations resulted in F_0 maternal doses of 0.8-0.9, 4.2-4.6, and 8.0-10.5 mg/kg/day, respectively, during gestation and 1.2-1.7, 5.6-8.3, and 13.7-19.1 mg/kg/day, respectively, during lactation. The developmental neurotoxicity of lindane was evaluated in the F_1 offspring. F_1 animals (10/sex) were evaluated for FOB, motor activity, auditory startle response, and learning and memory as well as developmental landmarks such as vaginal perforation and balanopreputial separation, and brain weights and histopathology on days 11 and 65, including morphometrics.

Small differences in absolute maternal body weights (7-8%) were observed between the high dose and control groups during gestation and early lactation (through day 11). Body weight gains by the high-dose dams from GD 6 through GD 20 were 64-79% (p # 0.01) of the control level. Body weight changes during lactation were similar between the treated and control groups. During gestation, food consumption by the high-dose group was significantly (p # 0.01; 74-92% of controls) less than the control group for the intervals of GD 10-13, 14-17, and 18-19. Food consumption by the low- and mid-dose groups during gestation and by all treated groups during lactation was similar to the controls.

Absolute body weights of the treated male and female pups in mid and high dose groups during lactation were 12-18% and 16-20% less than controls, respectively on days 4-11 of lactation with recovery to less than 10% by day 21. Body weight gains (p # 0.05 or 0.01) on lactation days 1-4 and 1-11 were 76% and 84%, respectively, of the control levels for mid-dose males, 79% and 79%, respectively, for mid-dose females, 60% and 73%, respectively for high-dose males, and 63 and 75%, respectively, for high-dose females. Body weight gains by all treated groups were similar to the controls during lactation days 11-21. Except for mid and high dose females, postweaning, body weight gains were similar between the treated and control groups. Body weight differences for high dose dams were 10% less at the beginning of lactation and recovered to 6% less by the end of the study.

The high-dose group had a greater number of stillborn pups as indicated by a live birth index of

77% compared with 99% for the control group. In addition, nine high-dose litters either died or were sacrificed moribund on lactation days 1-4. This resulted in a viability index for the high-dose group of 71% compared with 89% for the controls. Pup mortality in the mid and high-dose groups in litters surviving to weaning was greater before day 4 than in controls [3 pups in 2/20 controls; 18 pups in 8/22 litters, mid dose; 14 pups in 4/15 litters, high dose]. Survival was not affected at any time in the low dose group as compared with the control group. No dose- or treatment-related differences were observed between treated and control groups for duration of gestation, number of pups/litter on day 1, or per cent male offspring.

At necropsy, no treatment-related gross abnormalities were observed in the dams or offspring. Absolute and relative liver and kidney weights of the offspring were not affected by treatment.

A few clinical signs were observed in high dose dams and pups; increased reactivity to handling in dams on weeks 2 and 3 of dosing, and slower surface righting in pups on day 4. There were no effects on measures of physical or sexual development.

There was an increase in motor activity at the mid and high dose during lactation in both sexes. Some decrease in habituation of motor activity in females on day 22 was also seen. While there was no effect on auditory startle reflex amplitudes, there was a clear reduction in auditory startle response habituation in both sexes at the high dose on day 28 and on day 60. Slight decreases in absolute, but not relative, brain weights in mid and high dose female pups were observed on postnatal day 11 (9-10%) but narrowed to 3-5% less by day 65. Brain lengths and widths were similar between the treated and control pups. Morphometric brain measurements did not show any significant differences in the sizes of the neocortex, hippocampus, corpus callosum, or cerebellum on days 11 or 65. There were no effects on histopathology of the nervous system.

The maternal toxicity LOAEL is 120 ppm (13.7 mg/kg/day) based on decreased body weight gains, decreased food consumption, and increased reactivity to handling.

The maternal toxicity NOAEL is 50 ppm (5.6 mg/kg/day).

The offspring toxicity LOAEL is 50 ppm (5.6 mg/kg/day) based on reduced pup survival, decreased body weights and body weight gains during lactation, increased motor activity, and decreased motor activity habituation.

The offspring toxicity NOAEL is 10 ppm (1.2 mg/kg/day).

This study is classified as **Unacceptable/Guideline** [870.6300 (§83-6)] since laboratory validation studies of the neurobehavioral tests were not included, but it may be upgraded and found acceptable if this information is obtained. The number of animals tested at the highest dose is only 6 compared to the required number of 10 animals per dose.

4.9 Metabolism

Adequacy of data base for metabolism: The data base for metabolism is considered to be complete. No additional studies are required at this time. Lindane is distributed to all organs at measurable concentrations within a few hours after oral administration. The highest concentrations are found in adipose tissue. The metabolism of lindane is initiated through one of pathways: Dehydrogenation leading to (-HCH, Dehydrochlorination leading to formation of (-PCCH, Dechlorination leading to formation of (-tetrachlorohexene, or Hydroxylation leading to formation of hexachlorocyclohexanol. Further metabolism leads to a large number of metabolites. Volatilizalion appears to be an important route of its dissipation under the high-temperature conditions of tropical regions. Lindane is converted by enzymatic reactions, mainly in the liver. In mammals, including humans, lindane is excreted very rapidly in urine and faeces after metabolic degradation; only small amounts are eliminated unchanged. The half-life of lindane administered to rats is 2-4 days depending on the frequency of exposures, single or repeated.

870.7600 Dermal Absorption - Rat

EXECUTIVE SUMMARY: In a dermal absorption study, (MRID 40056107) 24 male Crl:CD®(SD)BR rats per group received dermal applications of lindane 20% emulsifiable concentrate ([^{14}C]-Lindane and unlabeled Lindane) at doses of 0.1, 1.0, or 10 mg/rat. Four animals/group were bled and sacrificed at intervals of 0.5, 1, 2, 4, 10, or 24 hours after application of the test article.

Quantities absorbed increased with dose and duration of exposure while percent absorbed increased with time and decreased with dose. Percents of the low-, mid-, and high-doses absorbed were 0.6, 0.96, and 0.66% after 0.5 hours; 18.07, 8.31, and 2.81% after 10 hours; and then, increased to 27.72, 20.86, and 5.05% after 24 hours. The total amount of test article absorbed after 24 hours, as calculated from urine, feces, and carcass, was 0.028, 0.21, and 0.51 mg for the low-, mid-, and high-dose groups, respectively. The process appears to be approaching saturation at the high dose. Recovered radioactivity (absorbed, skin, skin rinse, filter paper and spreader) was 74.19, 70.19 and 58.35% of the applied dose after 24 hours of exposure in the low-, mid-, and high-dose, respectively.

This study is considered **Acceptable/guideline** and satisfies the requirements for a dermal absorption study in rats [85-2].

EXECUTIVE SUMMARY: In a dermal absorption study, (MRID 40056108) 24 male Hra:(NZW)SPF rabbits per group received dermal applications of lindane 20% emulsifiable concentrate ([^{14}C]-Lindane and unlabeled Lindane) at doses of 0.5, 5.0, or 50 mg/rabbit. Four animals/group were bled and sacrificed at intervals of 0.5, 1, 2, 4, 10, or 24 hours after application of the test article.

Quantities absorbed increased with dose and duration of exposure while percent absorbed increased with time and decreased with dose. Percentages of the low-, mid-, and high-doses absorbed were 5.97, 6.68, and 1.99% after 0.5 hours ; 51.68, 23.76 and 10.96% after 10 hours; and then increased to 55.68, 39.99, and 16.56% after 24 hours. The total amount of test article absorbed after 24 hours, as calculated from urine, feces, and carcass, was 0.28, 2.00, and 8.46 mg for the low-, mid-, and high-dose groups, respectively. The original DER states that no evidence of saturation of the absorption process was observed; however upon further examination it appears that there is evidence of saturation at the highest dose (50 mg/rabbit) tested. Recovered radioactivity (absorbed, skin, skin rinse, filter paper and spreader) was 82.01, 78.27 and 66.34% of the applied dose after 24 hours of exposure in the low-, mid-, and high-dose, respectively.

This study is considered **Acceptable/guideline** and satisfies the requirements for a dermal absorption study in rabbits [85-2]. However, it should be noted that the rabbit is not the preferred species for dermal absorption studies as it grossly overestimates absorption compared to man.

5.0 TOXICITY ENDPOINT SELECTION

5.1 See Section 9.2 for Endpoint Selection Table.

5.2 Dermal Absorption

Dermal Absorption Factor: 10 %

The HIARC concurred with the TES committee decision (HED Doc. # 013460) that the dermal absorption factor is 10% based on a published report by Feldman and Maibach (Toxicology and Applied Pharmacology 28, 126-132, 1974).

The Maibach study tested 12 pesticides and herbicides, including lindane, on human subjects (6 per chemical) to quantitate their dermal penetration. C^{14}-labeled chemicals were applied topically ($4\mu g/cm^2$) to the forearm or via the intravenous route ($1\mu Ci$). Excretion of the chemicals was then monitored by collecting and analyzing urine samples during the 5 day testing period. All results were calculated as percent of the injected or applied dose. Data obtained after IV dosing was used to correct the skin penetration data for incomplete urinary recovery. Lindane was shown to have a penetration factor of 9.3% ± 3.7 (SD).

The dermal absorption factor is required for dermal exposure for all durations of exposure risk assessment since oral doses were selected for these exposure periods.

5.3 Classification of Carcinogenic Potential

The classification of carcinogenic potential will be re-evaluated upon receipt of a new mouse carcinogenicity study, expected in December 2000. Currently, according to the TES committee report (1994, Doc 013460), lindane has not been classified by the HED Cancer Peer Review Committee. The

RfD/Peer Review Committee in 1993 concluded that: "The mouse carcinogenicity data were considered insufficient because of major deficiencies associated with all studies available." Lindane however had been previously (1985) classified by the Cancer Assessment Group of the Office of Research and Development as a group B2/C carcinogen based on increased incidence of mouse liver tumors. Although the animal data was limited, the presence of a carcinogenic metabolite, 2,4,6-trichlorophenol, in meaningful quantities in the urine of humans exposed to lindane and the structural similarity with a rodent carcinogen, alpha-hexachlorocyclohexane, elevated the classification above a “C” to “B2". The upper-bound slope of the dose-response was $Q1^* = 1.1\ (mg/kg/day)^{-1}$.

6.0 FQPA CONSIDERATIONS

6.1 Special Sensitivity to Infants and Children

Although the developmental study in rats provided no indication of a quantitative increased susceptibility/sensitivity following *in utero* exposure to lindane, evidence of a qualitative increase in susceptibility was noted in the developmental neurotoxicity study and the 2-generation reproductive study in rats. Therefore, the FQPA committee decided to reduce the safety factor to 3X for lindane.

In the prenatal developmental toxicity studies in rats, developmental effects were observed only at or above doses causing maternal toxicity. The prenatal developmental study in rabbits is classified as Unacceptable (not upgradable) since maternal and developmental toxicity LOAELs were not identified and the highest dose did not approach the limit dose. Therefore, dose selection was considered inadequate. Doses were based on the results of a subcutaneous study in the rabbit (MRID 00062658) which is not a valid method for selecting doses for an oral study. Several other deficiencies were noted in the conduct of this study, included: percent purity of the test article was not given, dosing solutions were not analyzed for concentration, stability, or homogeneity, and much of the individual animal data were not included.

Although the developmental toxicity study in rabbits was classified unacceptable, the HIARC concluded that a new study is not required because: 1) The developmental toxicity study in rabbits and rats using a subcutaneous route of administration shows no developmental effects at the maternally toxic dose; 2) The incidences of skeletal effects observed in the developmental toxicity study in rats, with gavage as the route of administration, are within historical controls; 3) More severe maternal effects are seen in the rabbit study with subcutaneous administration; 4) The rat appears to be the more sensitive species for developmental effects; 5) A developmental neurotoxicity study has already been submitted.

There was, however, evidence of qualitative increased susceptibility in the rat multi-generation reproduction study: Both parental and offspring LOAELS are 13 mg/kg; however there is a qualitative difference in the severity of effects. In the parental animals, toxicity was seen in the form of reduction in body weight gain during gestation while offspring toxicity was correlated with decreases in pup viability and pup body weight in the F_1 and F_2 generations as well as delayed maturation in the F_2 generation. Evidence for quantitative increase in susceptibility could not be ascertained due to the wide spread in the doses tested.

There is also quantitative increased susceptibility demonstrated in the rat developmental neurotoxicity study: Maternal toxicity observed at 120 ppm (13.7 mg/kg/day, LOAEL) is based on decreased body weight gains, decreased food consumption, and increased reactivity to handling (maternal NOAEL is 50 ppm; 5.6 mg/kg/day). Offspring toxicity was observed at 50 ppm (5.6 mg/kg/day, LOAEL) and is based on reduced pup survival, decreased body weights and body weight gains during lactation, increased motor activity, and decreased motor activity habituation (NOAEL is 10 ppm; 1.2 mg/kg/day).

The offspring effects seen in the developmental neurotoxicity study were the same as those seen in the the two-generation reproduction study - no additional functional or morphological changes in the nervous system were noted. In the open literature, lindane is found in mother's milk and metabolites of lindane have been shown to cross the placental barrier.

6.2 Recommendation for a Developmental Neurotoxicity Study

A developmental neurotoxicity study has already been conducted.

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8.0 APPENDICES
Tables for Use in Risk Assessment

8.1 Toxicity Profile Summary Tables

8.1.1 Acute Toxicity Table - See Section 4.1

8.1.2 Subchronic, Chronic and Other Toxicity Tables

Table 1

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3250 90-Day dermal toxicity	41427601 acceptable/ guideline 1990	NOAEL = 60 mg/kg/day LOAEL = 10 mg/kg/day based on lesion in the liver in males and females and adrenal gland weight increases in males
870.3465 90-Day inhalation toxicity	00255003 acceptable/guideline 1983	NOAEL = 0.025 mg/kg/day LOAEL = 0.13 mg/kg/day based on transient microscopic lesions in the kidney and increased kidney weights in the males.
	40873501 acceptable/guideline 1988	NOAEL = 0.08 mg/kg/day LOAEL = 0.25 mg/kg/day based on death of one male and one female
870.3700a Prenatal developmental in rat	00062656 (Subcutaneous) unacceptable/ nonguideline 1976	**Maternal** NOAEL = 5 mg/kg/day LOAEL = 15 mg/kg/day based on reduced body weight **Developmental** NOAEL = >30 mg/kg/day LOAEL = not identified
	42808001 acceptable/ guideline 1971	**Maternal** NOAEL = 5 mg/kg/day LOAEL = 10 mg/kg/day based on reduced body weight and food consumption **Developmental** NOAEL = 10 mg/kg/day LOAEL = 20 mg/kg/day based on skeletal variation.
870.3700b Prenatal developmental in rabbit	00062658 (Subcutaneous) unacceptable/ nonguideline 1976	**Maternal** NOAEL = 5 mg/kg/day LOAEL = 15 mg/kg/day based on clinical signs, mortality, reduced body weight **Developmental** NOAEL \$15 mg/kg/day LOAEL = not identified
	42808002 unacceptable/ nonguideline 1971	**Maternal** NOAEL \$20 mg/kg/day LOAEL = not identified **Developmental** NOAEL \$20 mg/kg/day LOAEL = not identified

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3800 Reproduction and fertility effects	42246101 acceptable/ guideline 1991	NOAEL = 1.7 mg/kg/day &; 0.09mg/kg/day % LOAEL = 13 mg/kg/day based on reduced body weight &; 1.7 mg/kg/day based on increased kidney weight and alpha-2 globulin accumulation %
870.4100a Chronic toxicity rodents 870.4200 Carcinogenicity rats	41094101 41853701 42891201 acceptable/ guideline 1993	NOAEL =0.6 mg/kg/day LOAEL = 4.8 mg/kg/day %; 6 mg/kg/day & based on periacinar hepatocyte hypertrophy, increased liver and spleen weights, and decreased platelets **no evidence of carcinogenicity**
870.4300 Carcinogenicity mice	special study 1987	NOAEL = not identified LOAEL = 23 mg/kg/day based on induction of tumors, increased liver weights, increased enzyme activity, and irreversible Clara cell hyperplasia in lung **evidence of carcinogenicity-** liver and lung tumors
870.5300 Gene Mutation Mammalian Cell	00144500 unacceptable/guideline 1985	negative
870.5915 In Vivo Sister Chromatid Exchange	00024504 unacceptable guideline 1984	negative
870.5450 dominant lethal assay	00062657 unacceptable guideline	negative
870.6200a Acute neurotoxicity screening battery	44769201 acceptable/ guideline 1999	NOAEL = 6 mg/kg/day &; 20 mg/kg/day % LOAEL = 20 mg/kg/day based on icreased grip strength and motor activity. 60 mg/kg/day based on tremors, convulsions, decreased motor activity and increased grip strngth.
870.6200b Subchronic neurotoxicity screening battery	44781101 acceptable/ guideline 1999	NOAEL = 7.9 mg/kg/day&; 7.1 mg/kg/day% LOAEL = 30.2 mg/kg/day and 28.1 mg/kg/day based on hypersensitivity to touch and hunched posture

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.6300 Developmental neurotoxicity	45073501 unacceptable/guideline 1999	**Maternal** NOAEL = 5.6 mg/kg/day LOAEL = 13.7 mg/kg/day based on decreased body weight gains, decreased food consumption, and increased reactivity to handling. **Offspring** NOAEL = 1.2 mg/kg/day LOAEL = 5.6 mg/kg/day based on reduced pup survival, decreased body weights and body weight gains during lactation, increased motor activity, and decreased motor activity habituation.
870.7600 Dermal penetration	40056107-rat 40056108-rabbit acceptable/ guideline 1987	18 % absorption at 10 hours

Table 2 Summary of Toxicological Dose and Endpoints for LINDANE for Use in Human Risk Assessment[1]

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Endpoint for Risk Assessment	Study and Toxicological Effects
Acute Dietary females 13-50 years of age			not applicable; no relevant single exposure endpoint was identified
Acute Dietary general population including infants and children	NOAEL= 6 mg/kg/day UF = 100 **Acute RfD** = 0.06 mg/kg/day	FQPA SF = 3 **aPAD** = acute RfD / FQPA SF = 0.02 mg/kg/day	Acute Neurotoxicity in Rats/ MRID 44769201 LOAEL is 20 mg/kg based on increased grip strength, increased Motor Activity
Chronic Dietary all populations	NOAEL= 0.47 mg/kg/day UF = 100 **Chronic RfD** = 0.0047 mg/kg/day	FQPA SF = 3 **cPAD** = chr RfD / FQPA SF = 0.0016 mg/kg/day	Chronic Feeding and Carcinogenicity in Rats MRID 41094101, 41853701, 42891201 LOAEL is 4.81 mg/kg/day based on periacinar hepatocyte hypertrophy, increased liver/spleen weigt, increased platelets
Short-Term Dermal (1-7 days) (Occupational/ Residential)	oral study NOAEL= 1.2 mg/kg/day (dermal absorption rate = 10%)	**LOC for MOE** = 100 (Occupational) **no residential exposure expected**	Developmental Neurotoxicity Study in Rats (MRID 45073501) LOAEL is 5.6 mg/kg/day based on reduced pup survival, decreased body weights and body weight gains during lactation, increased motor activity, and decreased motor activity habituation

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Endpoint for Risk Assessment	Study and Toxicological Effects
Intermediate-Term Dermal (1 week - several months) (Occupational)	oral study NOAEL= 1.2 mg/kg/day (dermal absorption rate = 10%)	**LOC for MOE** = 100 (Occupational)	Developmental Neurotoxicity Study in Rats (MRID 45073501) LOAEL is 5.6 mg/kg/day based on reduced pup survival, decreased body weights and body weight gains during lactation, increased motor activity, and decreased motor activity habituation.
Long-Term Dermal (several months - lifetime) (Occupational)	oral study NOAEL= 0.47 mg/kg/day (dermal absorption rate = 10%)	**LOC for MOE** = 100 (Occupational)	Chronic Feeding and Carcinogenicity in Rats MRID 41094101, 41853701, 42891201 LOAEL is 4.81 mg/kg/day based on periacinar hepatocyte hypertrophy, increased liver/spleen weigt, increased platelets
Short-Term Inhalation (1-7 days) (Occupational)	inhalation study LOAEL= 0.13 mg/kg/day	**LOC for MOE** = 100 (Occupational)	90-Day Inhalation Toxicity MRID 00255003 based on clinical signs (diarrhea, piloerection) seen at day 14 and continuing for 20 days.
Intermediate-Term Inhalation (1 week - several months) (Occupational)	inhalation study NOAEL= 0.025 mg/kg/day	**LOC for MOE** = 100 (Occupational)	90-Day Inhalation Toxicity MRID 00255003 LOAEL is 0.13 mg/kg/day based on micro lesions in kidney, increased kidney weight
Cancer (oral)	group B2/C carcinogen	Q1* = 1.1 $(mg/kg/day)^{-1}$	based on increased incidence of mouse liver tumors

[1] UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, LOC = level of concern, MOE = margin of exposure

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